

OPANA - oxymorphone hydrochloride tablet

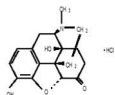
Endo Pharmaceuticals Inc.

DESCRIPTION

OPANA (oxymorphone hydrochloride) is a semi-synthetic opioid analgesic supplied in 5 mg and 10 mg tablet strengths for oral administration. The tablet strengths describe the amount of oxymorphone hydrochloride per tablet. The tablets contain the following inactive ingredients: lactose monohydrate, magnesium stearate, and pregelatinized starch. In addition, the 5 mg tablets contain FD&C blue No. 2 aluminum lake. The 10 mg tablets contain D&C red No. 30 aluminum lake.

Chemically, oxymorphone hydrochloride is 4, 5 α -epoxy-3, 14-dihydroxy-17-methylmorphinan-6-one hydrochloride, a white or slightly off-white, odorless powder, which is sparingly soluble in alcohol and ether, but freely soluble in water. The molecular weight of oxymorphone hydrochloride is 337.80. The pK_{a1} and pK_{a2} of oxymorphone at 37°C are 8.17 and 9.54, respectively. The octanol/aqueous partition coefficient at 37°C and pH 7.4 is 0.98.

The structural formula for oxymorphone hydrochloride is as follows:



CLINICAL PHARMACOLOGY

Oxymorphone is an opioid agonist whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, oxycodone, hydromorphone, fentanyl, codeine, hydrocodone and tramadol. In addition to analgesia, other pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

Central Nervous System

The precise mechanism of the analgesic action is unknown. However, specific CNS (central nervous system) opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug. In addition, opioid receptors have been identified within the PNS (peripheral nervous system). The role that these receptors play in these drugs' analgesic effects is unknown.

Opioids produce respiratory depression, likely by a direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

Opioids depress the cough reflex by direct effect on the cough center in the medulla oblongata. Antitussive effects may occur with doses lower than those usually required for analgesia. Opioids cause miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations (see **OVERDOSAGE: Signs and Symptoms**).

Gastrointestinal Tract and Other Smooth Muscle

Opioids cause a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasms of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Opioids produce peripheral vasodilation which may result in orthostatic hypotension. Release of histamine can occur and may contribute to opioid-induced hypotension. Manifestations of histamine release may include orthostatic hypotension, pruritus, flushing, red eyes, and sweating. Animal studies have shown that oxymorphone has a lower propensity to cause histamine release than other opioids.

Endocrine System

Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species, rats and dogs. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Immune System

Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown.

Pharmacodynamics

Concentration-Efficacy Relationships

Studies in healthy volunteers reveal predictable relationships between OPANA dosage and plasma oxymorphone concentrations.

The minimum effective plasma concentration of oxymorphone for analgesia varies widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients need to be individually titrated to achieve a balance between therapeutic and adverse effects. The minimum effective analgesic concentration of oxymorphone for any individual patient may increase over time due to an increase in pain, progression of disease, development of a new pain syndrome and/or development of analgesic tolerance.

Concentration-Adverse Experience Relationships

OPANA is associated with typical opioid-related adverse experiences. There is a general relationship between increasing opioid plasma concentration and increasing frequency of adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression.

As with all opioids, the dose must be individualized (see **DOSAGE AND ADMINISTRATION**). The effective analgesic dose for some patients will be too high to be tolerated by other patients.

Pharmacokinetics

Absorption

The absolute oral bioavailability of oxymorphone is approximately 10%.

Steady-state levels were achieved after 3 days of multiple dose administration. Under both single-dose and steady-state conditions, dose proportionality has been established for 5 mg, 10 mg and 20 mg doses of OPANA, for both peak plasma levels (C_{max}) and extent of absorption (AUC)(Table 1).

Table 1 Mean (\pm SD) OPANA Pharmacokinetic Parameters

Regimen	Dosage	C_{max} (ng/mL)	AUC (ng·hr/mL)	$T_{1/2}$ (hr)
Single Dose	5 mg	1.10 \pm 0.55	4.48 \pm 2.07	7.25 \pm 4.40
	10 mg	1.93 \pm 0.75	9.10 \pm 3.40	7.78 \pm 3.58
	20 mg	4.39 \pm 1.72	20.07 \pm 5.80	9.43 \pm 3.36
Multiple Dose ^a	5 mg	1.73 \pm 0.62	4.63 \pm 1.49	NA
	10 mg	3.51 \pm 0.91	10.19 \pm 3.34	NA
	20 mg	7.33 \pm 2.93	21.10 \pm 7.59	NA

NA= not applicable

Results after 5 days of every 6 hours dosing.

Food Effect

After oral dosing with 40 mg of OPANA in healthy volunteers under fasting conditions or with a high-fat meal, the C_{max} and AUC were increased by approximately 38% in fed subjects relative to fasted subjects. As a result, OPANA should be dosed at least one hour prior to or two hours after eating (see **DOSAGE AND ADMINISTRATION**).

Ethanol Effect

The effect of co-ingestion of alcohol with OPANA has not been evaluated. However, an *in vivo* study was performed to evaluate the effect of alcohol (40%, 20%, 4% and 0%) on the bioavailability of a single dose of 40 mg of OPANA ER (an extended-release

formulation of oxymorphone) in healthy, fasted volunteers. Following concomitant administration of 240 mL of 40% ethanol the C_{max} increased on average by 70% and up to 270% in individual subjects. Following the concomitant administration of 240 mL of 20% ethanol, the C_{max} increased on average by 31% and up to 260% in individual subjects. In some individuals there was also a decrease in oxymorphone peak plasma concentrations. No effect on the release of oxymorphone from OPANA ER was noted in an *in vitro* alcohol interaction study. The mechanism of the *in vivo* interaction is unknown. Therefore, co-administration of oxymorphone and ethanol must be avoided.

Distribution

Formal studies on the distribution of oxymorphone in various tissues have not been conducted. Oxymorphone is not extensively bound to human plasma proteins; binding is in the range of 10% to 12%.

Metabolism

Oxymorphone is highly metabolized, principally in the liver, and undergoes reduction or conjugation with glucuronic acid to form both active and inactive products. The two major metabolites of oxymorphone are oxymorphone-3-glucuronide and 6-OH-oxymorphone. The mean plasma AUC for oxymorphone-3-glucuronide is approximately 90-fold higher than the parent compound. The pharmacologic activity of the glucuronide metabolite has not been evaluated. 6-OH-oxymorphone has been shown in animal studies to have analgesic bioactivity. The mean plasma 6-OH-oxymorphone AUC is approximately 70% of the oxymorphone AUC following single oral doses but is essentially equivalent to the parent compound at steady-state.

Excretion

Because oxymorphone is extensively metabolized, <1% of the administered dose is excreted unchanged in the urine. On average, 33% to 38% of the administered dose is excreted in the urine as oxymorphone-3-glucuronide and 0.25% to 0.62% is excreted as 6-OH-oxymorphone in subjects with normal hepatic and renal function. In animals given radiolabeled oxymorphone, approximately 90% of the administered radioactivity was recovered within 5 days of dosing. The majority of oxymorphone-derived radioactivity was found in the urine and feces.

Special Populations

Elderly

The plasma levels of oxymorphone administered as an extended-release tablet were about 40% higher in elderly than in younger subjects.

Gender

The effect of gender on the pharmacokinetics of OPANA has not been studied. In a study with an extended-release formulation of oxymorphone, there was a consistent tendency for female subjects to have slightly higher AUC_{ss} and C_{max} values than male subjects. However, gender differences were not observed when AUC_{ss} and C_{max} were adjusted by body weight.

Hepatic Impairment

The liver plays an important role in the pre-systemic clearance of orally administered oxymorphone. Accordingly, the bioavailability of orally administered oxymorphone may be markedly increased in patients with moderate-severe liver disease. The effect of hepatic impairment on the pharmacokinetics of OPANA has not been studied. However, in a study with an extended-release formulation of oxymorphone, the disposition of oxymorphone was compared in 6 patients with mild, 5 patients with moderate, and one patient with severe hepatic impairment, and 12 subjects with normal hepatic function. The bioavailability of oxymorphone was increased by 1.6-fold in patients with mild hepatic impairment and by 3.7-fold in patients with moderate hepatic impairment. In one patient with severe hepatic impairment, the bioavailability was increased by 12.2-fold. The half-life of oxymorphone was not significantly affected by hepatic impairment.

Renal Impairment

The effect of renal impairment on the pharmacokinetics of OPANA has not been studied. However, in a study with a extended-release formulation of oxymorphone, an increase of 26%, 57%, and 65% in oxymorphone bioavailability was observed in mild (creatinine clearance 51-80 mL/min; n=8), moderate (creatinine clearance 30-50 mL/min; n=8), and severe (creatinine clearance <30 mL/min; n=8) patients, respectively, compared to healthy controls.

Drug-Drug Interactions

In vitro studies revealed little to no biotransformation of oxymorphone to 6-OH-oxymorphone by any of the major cytochrome P450 (CYP P450) isoforms at therapeutically relevant oxymorphone plasma concentrations.

No inhibition of any of the major CYP P450 isoforms was observed when oxymorphone was incubated with human liver microsomes at concentrations of ≤ 50 μ M. An inhibition of CYP 3A4 activity occurred at oxymorphone concentrations ≥ 150 μ M. Therefore, it is not expected that oxymorphone, or its metabolites will act as inhibitors of any of the major CYP P450 enzymes *in vivo*.

Increases in the activity of the CYP 2C9 and CYP 3A4 isoforms occurred when oxymorphone was incubated with human hepatocytes. However, clinical drug interaction studies with OPANA ER showed no induction of CYP450 3A4 or 2C9 enzyme activity, indicating that no dose adjustment for CYP 3A4- or 2C9-mediated drug-drug interactions is required.

CLINICAL TRIALS

The analgesic efficacy of OPANA has been evaluated in acute pain following orthopedic and abdominal surgeries.

Orthopedic Surgery

Two double-blind, placebo-controlled, dose-ranging studies evaluated the analgesic efficacy of doses of 10, 20, and 30 mg OPANA in patients with acute moderate to severe pain following orthopedic surgery. Efficacy was replicated for the 20 mg dose. OPANA 20 mg provided greater analgesia as measured by total pain relief compared to placebo. In one study, the mean total pain relief (0–5 categorical scale) over 8 hours was 12.3 ± 8.7 and 7.3 ± 7.6 , respectively. In a second study, the mean total pain relief over 8 hours was 12.6 ± 7.5 and 7.1 ± 5.8 for the OPANA 20 mg and placebo groups. OPANA 10 mg also provided greater analgesia as compared to placebo in the second study with mean total pain relief over 8 hours of 10.8 ± 7.4 . There was no evidence of superiority of the 30 mg dose over the 20 mg dose. However there was an unacceptably high rate of use of naloxone in patients receiving the OPANA 30 mg dose in the post-operative period (see **DOSAGE AND ADMINISTRATION**).

Abdominal Surgery

In a randomized, double-blind, placebo-controlled, multiple-dose study, the efficacy of OPANA 10 and 20 mg were assessed in patients with moderate to severe acute pain following abdominal surgery. In this study, patients were required to dose every 4 to 6 hours over a 48-hour treatment period. Time to early discontinuation was longer in both OPANA 10 and 20 mg treatment groups compared to the placebo group. The median times to discontinuation were 17 hours and 55 minutes for the OPANA 10 mg group, 20 hours and 15 minutes for the OPANA 20 mg group and 4 hours and 50 minutes for the placebo group (see **DOSAGE AND ADMINISTRATION**).

INDICATIONS AND USAGE

OPANA is indicated for the relief of moderate to severe acute pain where the use of an opioid is appropriate.

CONTRAINDICATIONS

OPANA should not be administered to patients with a known hypersensitivity to oxymorphone hydrochloride or to any of the other ingredients in OPANA, or with known hypersensitivity to morphine analogs such as codeine.

OPANA is contraindicated in patients with respiratory depression except in monitored settings and in the presence of resuscitative equipment and in patients with acute or severe bronchial asthma or hypercarbia. OPANA is contraindicated in any patient who has or is suspected of having paralytic ileus.

OPANA is contraindicated in patients with moderate and severe hepatic impairment (see **CLINICAL PHARMACOLOGY, PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

WARNINGS

OPANA is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Respiratory Depression

Respiratory depression is the chief hazard of OPANA. Respiratory depression is a particular potential problem in elderly or debilitated patients as well as in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

OPANA should be administered with extreme caution to patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, CNS depression or coma. In these patients, even usual therapeutic doses of oxymorphone may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea. Alternative non-opioid analgesics should be considered, and oxymorphone should be employed only under careful medical supervision at the lowest effective dose in such patients.

Misuse, Abuse and Diversion of Opioids

OPANA contains oxymorphone, an opioid agonist with an abuse liability similar to morphine and a Schedule II controlled substance. Opioid agonists have the potential for being abused and are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing oxymorphone in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OPANA tablets may be abused by crushing, chewing, snorting or injecting the product. These practices pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS: Drug Abuse and Addiction**).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse

Oxymorphone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation or coma may result.

Drug Abuse and Addiction

Controlled Substance

OPANA contains oxymorphone, an opioid with an abuse liability similar to morphine and other opioids and is a Schedule II controlled substance. Oxymorphone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion (see **WARNINGS: Misuse, Abuse and Diversion of Opioids**).

Drug addiction is characterized by a preoccupation with the procurement, hoarding, and abuse of drugs for non-medicinal purposes. Drug addiction is treatable, utilizing a multi-disciplinary approach, but relapse is common.

“Drug seeking” behavior is very common to addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of loss of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. OPANA, like other opioids, may be diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Abuse of OPANA poses a risk of overdose and death. This risk is increased with concurrent abuse of OPANA with alcohol and other substances. In addition, parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms (see **PRECAUTIONS: Pregnancy** and **PRECAUTIONS: Labor and Delivery**).

Interactions with Other Central Nervous System Depressants

Patients receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with oxymorphone may exhibit an additive CNS depression (see **PRECAUTIONS: Drug-Drug Interactions**). Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual dose of OPANA.

Head Injury and Increased Intracranial Pressure

In the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure, the possible respiratory depressant effects of opioid analgesics and their potential to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO₂ retention) may be markedly exaggerated. Furthermore, opioid analgesics can produce effects on pupillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Hypotensive Effect

OPANA, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. OPANA, like all opioid analgesics, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

Hepatic Impairment

A study of OPANA ER in patients with hepatic disease indicated greater plasma concentrations than those with normal hepatic function (see **CLINICAL PHARMACOLOGY**). OPANA should be used with caution in patients with mild impairment. These patients should be started with the lowest dose and titrated slowly while carefully monitoring for side effects. OPANA is

contraindicated for patients with moderate and severe hepatic impairment (see **CONTRAINDICATIONS, WARNINGS, and DOSAGE AND ADMINISTRATION**).

PRECAUTIONS

General

Opioid analgesics should be used with caution, especially when combined with other drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known potential risks of respiratory depression, altered mental state and postural hypotension. OPANA should be used with caution in elderly and debilitated patients and in patients who are known to be sensitive to central nervous system depressants, such as those with cardiovascular, pulmonary, renal, or hepatic disease.

OPANA should be used with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of pulmonary or renal function; moderate impairment of hepatic function; and toxic psychosis.

The administration of all opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions. All opioids may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxymorphone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxymorphone and/or may precipitate withdrawal symptoms in these patients.

Ambulatory Surgery and Post-Operative Use

OPANA, like other opioids, decreases bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

Use in Pancreatic/Biliary Tract Disease

OPANA, like other opioids, may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis.

Physical Dependence and Tolerance

Physical dependence is the occurrence of withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an opioid antagonist or mixed opioid agonist/antagonist agent. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). The development of physical dependence and/or tolerance is not unusual during chronic opioid therapy.

If OPANA is abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, OPANA should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION: Cessation of Therapy**).

Information for Patients/Caregivers

1. Patients should be advised that OPANA contains oxymorphone, which is a morphine-like pain reliever, and should be taken only as directed.
2. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy to their doctor. Individualization of dosage is essential to make optimal use of this medication.
3. Patients should be advised not to adjust the dose of OPANA without consulting the prescribing professional.
4. Patients should be cautioned that OPANA may cause drowsiness, dizziness, or lightheadedness and may impair mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car, operating machinery, etc.
5. OPANA will add to the effect of alcohol and other CNS depressants (such as antihistamines, sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and monoamine oxidase [MAO] inhibitors).
6. Patients should not combine OPANA with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.

7. Patients taking OPANA should be advised of the potential for severe constipation. Appropriate laxatives and/or stool softeners and other therapeutic approaches should be considered for use with the initiation of OPANA therapy.
8. Women of childbearing potential who become or are planning to become pregnant should be advised to consult their physician regarding the effects of opioid analgesics and other drug use during pregnancy on themselves and their unborn child.
9. Safe use in pregnancy has not been established. Prolonged use of opioid analgesics during pregnancy may cause fetal-neonatal physical dependence, and neonatal withdrawal may occur.
10. Patients should be advised that if they have been receiving treatment with OPANA for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the OPANA dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.
11. Patients should be advised that OPANA is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
12. Patients should be instructed to keep OPANA in a secure place out of the reach of children and pets. Accidental consumption especially in children may result in overdose or death. When OPANA is no longer needed, the unused tablets should be destroyed by flushing down the toilet.

Use in Drug and Alcohol Addiction

OPANA is not approved for use in detoxification or maintenance treatment of opioid addiction. However, the history of an addictive disorder does not necessarily preclude the use of this medication for the treatment of chronic pain. These patients will require intensive monitoring for signs of misuse, abuse, or addiction.

Drug-Drug Interactions

Oxymorphone is highly metabolized principally in the liver and undergoes reduction or conjugation with glucuronic acid to form both active and inactive products (see **CLINICAL PHARMACOLOGY** and **Pharmacokinetics: Metabolism**).

Use with CNS Depressants

The concomitant use of other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol may produce additive CNS depressant effects. OPANA, like all opioid analgesics, should be started at 1/3 to 1/2 of the usual dose in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result and titrated slowly as necessary for adequate pain relief.

Additive effects resulting in respiratory depression, hypotension, profound sedation or coma may result if these drugs are taken in combination with the usual doses of OPANA. No specific interaction between oxymorphone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

When combined therapy with any of the above medications is contemplated, the dose of one or both agents should be reduced (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

Use with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, or buprenorphine) should not be administered to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic, such as OPANA. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of OPANA and/or may precipitate withdrawal symptoms.

Other

Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

In addition, CNS side effects have been reported (confusion, disorientation, respiratory depression, apnea, seizures) following coadministration of cimetidine with opioid analgesics; a causal relationship has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Long-term studies have been completed to evaluate the carcinogenic potential of oxymorphone in both Sprague-Dawley rats and CD-1 mice. Oxymorphone HCl was administered to Sprague-Dawley rats (2.5, 5, and 10 mg/kg/day in males and 5, 10, and 25 mg/kg/day in females) for 2 years by oral gavage. The systemic drug exposure (AUC ng•h/mL) at the 10 mg/kg/day dose in male rats was 0.34-fold and at the 25 mg/kg/day dose in female rats was 1.5-fold the human exposure at a dose of 260 mg/day. No evidence of carcinogenic potential was observed in rats. Oxymorphone HCl was administered to CD-1 mice (10, 25, 75 and 150 mg/kg/day) for 2 years by oral gavage. The systemic drug exposure (AUC ng•h/mL) at the 150 mg/kg/day dose in mice was 14.5-fold

(in males) and 17.3-fold (in females) times the human exposure at a dose of 260 mg/day. No evidence of carcinogenic potential was observed in mice.

Mutagenesis: Oxymorphone hydrochloride was not mutagenic when tested in the *in vitro* bacterial reverse mutation assay (Ames test) at concentrations of ≤ 5270 mg/plate, or in an *in vitro* mammalian cell chromosome aberration assay performed with human peripheral blood lymphocytes at concentrations ≤ 5000 mg/ml with or without metabolic activation. Oxymorphone hydrochloride tested positive in both the rat and mouse *in vivo* micronucleus assays. An increase in micronucleated polychromatic erythrocytes occurred in mice given doses of ≥ 250 mg/kg and in rats given doses of 20 and 40 mg/kg. A subsequent study demonstrated that oxymorphone hydrochloride was not aneugenic in mice following administration of up to 500 mg/kg. Additional studies indicate that the increased incidence of micronucleated polychromatic erythrocytes in rats may be secondary to increased body temperature following oxymorphone administration. Doses associated with increased micronucleated polychromatic erythrocytes also produce a marked, rapid increase in body temperature. Pretreatment of animals with sodium salicylate minimized the increase in body temperature and prevented the increase in micronucleated polychromatic erythrocytes after administration of 40 mg/kg oxymorphone.

Impairment of fertility: Oxymorphone hydrochloride did not affect reproductive function or sperm parameters in male rats at any dose tested (≤ 50 mg/kg/day). In female rats, an increase in the length of the estrus cycle and decrease in the mean number of viable embryos, implantation sites and corpora lutea were observed at doses of oxymorphone ≥ 10 mg/kg/day. The dose of oxymorphone associated with reproductive findings in female rats is 0.8 times a total human daily dose of 120 mg based on a body surface area. The dose of oxymorphone that produced no adverse effects on reproductive findings in female rats (i.e., NOAEL) is 0.4-times a total human daily dose of 120 mg based on body surface area.

Pregnancy

The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on fetal development. The use of OPANA in pregnancy, in nursing mothers, or in women of child-bearing potential requires that the possible benefits of the drug be weighted against the possible hazards to the mother and the child (see **PRECAUTIONS**).

Teratogenic Effects

Pregnancy Category C

Oxymorphone hydrochloride administration did not cause malformations at any doses evaluated during developmental toxicity studies in rats (≤ 25 mg/kg/day) or rabbits (≤ 50 mg/kg/day). These doses are ~ 2 times and 8 times a total human daily dose of 120 mg, based on body surface area. There were no developmental effects in rats treated with 5 mg/kg/day or rabbits treated with 25 mg/kg/day. Fetal weights were reduced in rats and rabbits given doses of ≥ 10 mg/kg/day and 50 mg/kg/day, respectively. These doses are ~ 0.8 and 4 times respectively a total human daily dose of 120 mg, based on body surface area. There were no effects of oxymorphone hydrochloride on intrauterine survival at doses ≤ 25 mg/kg/day in rats, or ≤ 50 mg/kg/day in rabbits (see Non-teratogenic Effects, below). In a study that was conducted prior to the establishment of Good Laboratory Practices (GLP) and not according to current recommended methodology, a single subcutaneous injection of oxymorphone hydrochloride on gestation day 8 was reported to produce malformations in offspring of hamsters that received 10 times a total human daily dose of 120 mg based on body surface area. This dose also produced 83% maternal lethality.

There are no adequate and well-controlled studies in pregnant women. OPANA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects

Oxymorphone hydrochloride administration to female rats during gestation in a pre- and postnatal developmental toxicity study reduced mean litter size (18%) at a dose of 25 mg/kg/day, attributed to an increase in the incidence of stillborn pups. An increase in neonatal death occurred at doses ≥ 5 mg/kg/day. Post-natal survival of the pups was reduced throughout weaning following treatment of the dams with 25 mg/kg/day. Low pup birth weight and decreased postnatal weight gain occurred in pups born to oxymorphone-treated female rats given a dose of 25 mg/kg/day. This dose is ~ 2 times a total human daily dose of 120 mg, based on body surface area.

Prolonged use of opioid analgesics during pregnancy may cause fetal-neonatal physical dependence. Neonatal withdrawal may occur. Symptoms usually appear during the first days of life and may include convulsions, irritability, excessive crying, tremors, hyperactive reflexes, fever, vomiting, diarrhea, sneezing, yawning, and increased respiratory rate.

Labor and Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. OPANA is not recommended for use in women during and immediately prior to labor, when use of shorter acting analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased

rate of cervical dilatation, which tends to shorten labor. Neonates whose mothers received opioid analgesics during labor should be observed closely for signs of respiratory depression. A specific opioid antagonist, such as naloxone or nalmeferene, should be available for reversal of opioid-induced respiratory depression in the neonate.

Nursing Mothers

It is not known whether oxymorphone is excreted in human milk. Because many drugs, including some opioids, are excreted in human milk, caution should be exercised when OPANA is administered to a nursing woman. Ordinarily, nursing should not be undertaken while a patient is receiving oxymorphone because of the possibility of sedation and/or respiratory depression in the infant.

Pediatric Use

Safety and effectiveness of OPANA in pediatric patients below the age of 18 years have not been established.

Geriatric Use

OPANA should be used with caution in elderly patients. The plasma levels of oxymorphone are about 40% higher in elderly (≥ 65 years of age) than in younger subjects (see **CLINICAL PHARMACOLOGY**).

Of the total number of subjects in clinical studies of OPANA, 31 percent were 65 and over, while 7 percent were 75 and over. No overall differences in effectiveness were observed between these subjects and younger subjects. There were several adverse events that were more frequently observed in subjects 65 and over compared to younger subjects. These adverse events included dizziness, somnolence, confusion, and nausea. In general, dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Hepatic Impairment

A study of OPANA ER in patients with hepatic disease indicated greater plasma concentrations than those with normal hepatic function (see **CLINICAL PHARMACOLOGY**). OPANA should be used with caution in patients with mild impairment.

These patients should be started with the lowest dose and titrated slowly while carefully monitoring for side effects. OPANA is contraindicated for patients with moderate and severe hepatic impairment (see **CONTRAINDICATIONS, WARNINGS, and DOSAGE AND ADMINISTRATION**).

Renal Impairment

In a study of OPANA ER, patients with moderate to severe renal impairment were shown to have an increase in bioavailability ranging from 57-65% (see **CLINICAL PHARMACOLOGY**). These patients should be started cautiously with lower doses of OPANA and titrated slowly while carefully monitoring for side effects (see **DOSAGE AND ADMINISTRATION**).

Gender Differences

In clinical trials with OPANA, the overall incidence rates for one or more adverse events were similar among females and male subjects receiving OPANA and placebo.

ADVERSE REACTIONS

Adverse Reactions Reported in Placebo-Controlled Trials

The following table lists adverse reactions that were reported in at least 2% of patients in placebo-controlled trials.

MedDRA Preferred Term	OPANA (N=557)	Placebo (N=270)
Nausea	19.0%	11.5%
Pyrexia	14.2%	8.1%
Somnolence	9.3%	2.2%
Vomiting	9.0%	7.0%
Pruritus	7.9%	3.7%
Headache	6.8%	4.4%
Dizziness (Exc Vertigo)	6.5%	2.2%
Constipation	4.1%	1.1%
Confusion	2.7%	0.7%

Adverse Reactions Reported in All Clinical Trials

A total of 591 patients were treated with OPANA in the Phase 2/3 controlled clinical trials. The clinical trials consisted of patients with acute post-operative pain (n=557) and cancer pain (n=34) trials.

The adverse reactions are presented in the following manner: most common, common, and less common adverse reactions.

The **most common** adverse drug reactions ($\geq 10\%$) reported at least once by patients treated with OPANA in the clinical trials were nausea and pyrexia.

The **common** ($\geq 1\%$ - $< 10\%$) adverse drug reactions reported at least once by patients treated with OPANA in the clinical trials organized by MedDRA's (Medical Dictionary for Regulatory Activities) System Organ Class were:

Cardiac disorders: tachycardia

Gastrointestinal disorders: vomiting, constipation, dry mouth, abdominal distention, and flatulence

General disorders and administration site conditions: sweating increased

Nervous system disorders: dizziness (exc vertigo), somnolence, headache, anxiety, and sedation

Psychiatric disorders: confusion

Respiratory, thoracic and mediastinal disorders: hypoxia

Skin & subcutaneous tissue disorders: pruritus

Vascular disorders: hypotension

Other **less common** adverse reactions known with opioid treatment that were seen $< 1\%$ in the OPANA trials include the following:

Abdominal pain, agitation, allergic reactions, vision blurred, bradycardia, central nervous system depression, clamminess, appetite decreased, dehydration, depressed level of consciousness, depression, dermatitis, diarrhoea, difficult micturition, disorientation, dyspepsia, dysphoria, dyspnea, edema, euphoric mood, fatigue, feeling jittery, flushing, hallucination, hot flashes, hypersensitivity, hypertension, ileus, insomnia, lethargy, mental impairment, mental status changes, miosis, nervousness, oxygen saturation decreased, palpitation, postural hypotension, respiratory depression, respiratory distress, respiratory rate decreased, restlessness, syncope, urinary retention, urticaria, visual disturbances, weakness, and weight decreased.

OVERDOSAGE

Signs and Symptoms

Acute overdosage with OPANA is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest, and death may occur.

OPANA may cause miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations (see **CLINICAL PHARMACOLOGY: Central Nervous System**).

Treatment

In the treatment of OPANA overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation. Elimination or evacuation of gastric contents may be necessary in order to eliminate unabsorbed drug.

Before attempting treatment by gastric emptying or activated charcoal, care should be taken to secure the airway.

The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression, which may result from overdosage or unusual sensitivity to opioids including OPANA. Therefore, an appropriate dose of naloxone hydrochloride should be administered (usual initial adult dose 0.4 mg-2 mg) preferably by the intravenous route and simultaneously with efforts at respiratory resuscitation.

Nalmefene is an alternative pure opioid antagonist, which may be administered as a specific antidote to respiratory depression resulting from opioid overdose. Since the duration of action of OPANA may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered according to the antagonist labeling as needed to maintain adequate respiration.

In patients receiving OPANA, opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression. They should be administered cautiously to persons who are known, or suspected to be, physically dependent on any opioid agonist including OPANA. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. If respiratory depression is associated with muscular rigidity, administration of a neuromuscular blocking agent may be necessary to facilitate assisted or controlled ventilation. Muscular rigidity may also respond to opioid antagonist therapy.

DOSAGE AND ADMINISTRATION

OPANA is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine and other opioids.

OPANA, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

Selection of patients for treatment with OPANA should be governed by the same principles that apply to the use of similar opioid analgesics (see **INDICATIONS AND USAGE**). Physicians should individualize treatment in every case (see **DOSAGE AND ADMINISTRATION**), using non-opioid analgesics, prn opioids and/or combination products, and chronic opioid therapy in a

progressive plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality, and the American Pain Society.

As with any opioid drug product, it is necessary to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. In the selection of the initial dose of OPANA, attention should be given to the following:

1. The total daily dose, potency and specific characteristics of the opioid the patient has been taking previously;
2. The relative potency estimate used to calculate the equivalent oxymorphone dose needed;
3. The patient's degree of opioid tolerance;
4. The age, general condition, and medical status of the patient;
5. Concurrent non-opioid analgesic and other medications;
6. The type and severity of the patient's pain;
7. The balance between pain control and adverse experiences;
8. Risk factors for abuse, addiction or diversion, including a prior history of abuse, addiction or diversion.

The following dosing recommendations, therefore, can only be considered as suggested approaches to what is actually a series of clinical decisions over time in the management of the pain of each individual patient.

OPANA should be administered on an empty stomach, at least one hour prior to or two hours after eating (see PHARMACOKINETICS: Food Effect).

Initiation of Therapy

Opioid-Naïve Patients

Patients who have not been receiving opioid analgesics should be started on OPANA in a dosing range of 10 to 20 mg every four to six hours depending on the initial pain intensity. If deemed necessary to initiate therapy at a lower dose, patients may be started with OPANA 5 mg. The dose should be titrated based upon the individual patient's response to their initial dose of OPANA. This dose can then be adjusted to an acceptable level of analgesia taking into account the pain intensity and side effects experienced by the patient.

Initiation of therapy with doses higher than 20 mg is not recommended because of potential serious side effects (see Clinical Trials: Orthopedic Surgery).

Conversion from Parenteral Oxymorphone to OPANA

Given the absolute oral bioavailability of approximately 10%, patients receiving parenteral oxymorphone may be converted to OPANA by administering 10 times the patient's total daily parenteral oxymorphone dose as OPANA, in four or six equally divided doses (e.g. IV dose x 10/4). For example, approximately 10 mg of OPANA may be required to provide pain relief equivalent to a total daily IM dose of 4 mg oxymorphone. The dose can be titrated to optimal pain relief or combined with acetaminophen/NSAIDs for optimal pain relief. Due to patient variability with regard to opioid analgesic response, upon conversion patients should be closely monitored to ensure adequate analgesia and to minimize side effects.

Conversion from Other Oral Opioids to OPANA

For conversion from other opioids to OPANA, physicians and other healthcare professionals are advised to refer to published relative potency information, keeping in mind that conversion ratios are only approximate. In general, it is safest to start the OPANA therapy by administering half of the calculated total daily dose of OPANA in 4 to 6 equally divided doses, every 4-6 hours. The initial dose of OPANA can be gradually adjusted until adequate pain relief and acceptable side effects have been achieved.

Individualization of Dose

Once therapy is initiated, pain relief and other opioid effects should be frequently assessed. Patients should be titrated to adequate pain relief (generally mild or no pain). Patients who experience breakthrough pain may require dosage adjustment or non-opioid therapy such as acetaminophen or NSAIDs.

If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. Dose adjustments should be made to obtain an appropriate balance between pain relief and opioid-related adverse experiences. If significant adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated aggressively. Once adverse events are under control, upward titration should continue to an acceptable level of pain control.

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the healthcare team, the patient, and the caregiver/family. Patients and family members should be advised of the potential common side effects to decrease fear of the use of opioids and promote their optimal use.

Patients with Hepatic Impairment

OPANA is contraindicated in patients with moderate and severe hepatic dysfunction. OPANA should be used with caution in patients with mild hepatic impairment. These patients with mild hepatic impairment should be started with the lowest dose and titrated slowly while carefully monitoring side effects (see **CLINICAL PHARMACOLOGY**, **CONTRAINDICATIONS**, and **PRECAUTIONS**).

Patients with Renal Impairment

There are 57% and 65% increases in oxymorphone bioavailability in patients with moderate to severe renal impairment, respectively, treated with OPANA ER (see **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**). Accordingly, OPANA should be administered cautiously and in reduced dosages to patients with creatinine clearance rate less than 50 mL/min.

Use with CNS depressants

OPANA, like all opioid analgesics, should be started at 1/3 to 1/2 of the usual dose in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, and alcohol, because respiratory depression, hypotension and profound sedation or coma may result. No specific interaction between oxymorphone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate (see **PRECAUTIONS: General** and **PRECAUTIONS: Drug-Drug Interactions**).

Geriatrics

Caution should be exercised in the selection of the starting dose of OPANA for an elderly patient starting at the low end of the dosing range.

Maintenance of Therapy

OPANA is intended as an opioid analgesic for the management of moderate to severe acute pain where the use of an opioid analgesic is appropriate. During therapy, continual re-evaluation of the patient receiving OPANA is important, with special attention to the maintenance of pain control and the relative incidence of side effects associated with therapy. If the level of pain increases, effort should be made to identify the source of increased pain, while adjusting the dose and/or using adjuvant analgesics such as acetaminophen or NSAIDs.

Cessation of Therapy

When the patient no longer requires therapy with OPANA, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

SAFETY AND HANDLING

OPANA contains oxymorphone, which is a controlled substance. Oxymorphone is controlled under Schedule II of the Controlled Substances Act. Oxymorphone, like all opioids, is liable to diversion and misuse and should be handled accordingly. Patients and their families should be instructed to flush any OPANA tablets that are no longer needed.

OPANA may be targeted for theft and diversion. Healthcare professionals should contact their State Medical Board, State Board of Pharmacy, or State Control Board for information on how to detect or prevent diversion of this product.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].

Dispense in tight container as defined in the USP, with a child-resistant closure (as required).

HOW SUPPLIED

OPANA tablets are supplied as follows:

5 mg Tablet:

Blue, round, convex tablets debossed with E612 over 5 on one side and plain on the other.

Bottles of 100 tablets with child-resistant closure NDC 63481-612-70

Unit-Dose package of 100 tablets (5 blister cards of 20 tablets, not child-resistant, for hospital use only) NDC 63481-612-75

10 mg Tablet:

Red, round, convex tablets debossed with E613 over 10 on one side and plain on the other.

Bottles of 100 tablets with child-resistant closure NDC 63481-613-70

Unit-Dose package of 100 tablets (5 blister cards of 20 tablets, not child-resistant, for hospital use only) NDC 63481-613-75

Rx Only

DEA Order Form Required.

Manufactured for:

Endo Pharmaceuticals Inc.

Chadds Ford, Pennsylvania 19317

Manufactured by:

Novartis Consumer Health Inc.

Lincoln, NE 68517

